REMARKS

Further and favorable reconsideration is respectfully requested in view of the foregoing amendments and the following remarks.

Claims 1-6 are pending in this application.

Claim 1 is amended to recite a support layer hardly soluble or insoluble in water "comprising ethyl cellulose and hydroxypropyl cellulose." Support for this amendment can be found at page 8, lines 10-12 and 18-22, and page 10, line 27. Other changes of a minor nature have been made in claim 1, changing "contains" to "comprises", and inserting "agent" after "adhesive".

Claim 6 is amended to add "agent" after "adhesive", replace "optionally" with "further," and to replace "sweeting agent" with "sweetening agent."

Applicants respectfully submit that these amendments should be entered even though they are presented after a final rejection. The effect of the amendments is to clearly place the application in condition for allowance, as will be apparent from the following remarks.

I. Claim Rejection Under 35 U.S.C. § 112

The Examiner rejects claim 6 under 35 U.S.C. § 112, second paragraph, as being indefinite. Although not admitting to the propriety of the rejection, by this Amendment, "optionally" has been changed to "further," which is consistent with the "consists of" language of claim 6. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

II. Claim Rejections Under 35 U.S.C. § 103

The Examiner rejects claims 1, 4 and 6 under 35 U.S.C. § 103(a) as being unpatentable over Kim et al. (WO 01/87276) in view of Brantl et al. (U.S. 4,826,686) and further in view of McQuinn (U.S. 5,113,860). Applicants respectfully traverse the rejection.

The Present Invention

The subject matter of newly amended claim 1 of the present application is a patch containing fentanyl for the mucous membrane of the oral cavity, which comprises a drug layer, a support layer hardly soluble or insoluble in water **comprising ethyl cellulose and hydroxypropyl cellulose,** on the drug layer, and a backing on the support layer, wherein the drug layer contains fentanyl or its salt as an active ingredient, methyl vinyl ether-maleic anhydride

copolymer as an adhesive, and at least one substance selected from the group consisting of hydroxypropyl cellulose, hydroxypropyl methylcellulose and hydroxyethyl cellulose as a thickener.

The patch of the present invention (1) does not need any complex procedures when it is applied; (2) gives only a little uncomfortable feeling in the oral cavity; (3) can quickly increase the serum concentration as the drug is almost absorbed at the applied region; (4) makes less transfer of the drug into a gastrointestinal tract by preventing the drug's release into parts of the oral cavity except the applied region; (5) is easily torn off when it becomes unnecessary; (6) can easily control the serum concentration of the drug; (7) is usable as a rescue preparation for pang during the therapy for cancer pain; and (8) is very safe.

The present inventors found that a drug layer which contains fentanyl or its salt as an active ingredient, methyl vinyl ether-maleic anhydride copolymer as an adhesive (5 to 90 wt/%), and at least one substance selected from the group consisting of hydroxypropyl cellulose (HPC), hydroxypropyl methylcellulose (HPMC) and hydroxyethyl cellulose (HEC) as a thickener (0.2 to 80 wt/%) shows sufficient adhesivity to the mucous membrane of the oral cavity due to the presence of water, easily releases the drug from the applied surface, and quickly increases the serum concentration.

Furthermore, by laminating a support layer which is insoluble or hardly soluble in water comprising **ethyl cellulose and hydroxypropyl cellulose** on the opposite side of the adhesive surface of the drug layer, the drug is hardly swallowed with saliva, and thus is not released into regions in the oral cavity other than the applied region. Furthermore, by equipping a backing thereto, and making the patch thick regardless of its small size, the handling of the patch (such as picking it up, applying it, and tearing it off) is easy. Moreover, the patch containing fentanyl for the mucous membrane of the oral cavity easily controls the serum concentration.

The excellent effects of the present invention can be seen in Tests 1-4 and Figures 2-5 of the application, which show, for example, that the patch containing fentanyl for the mucous membrane of the oral cavity showed better skin-permeability effects compared with the control groups.

Kim et al.

First, Kim et al. do not teach or suggest a patch comprising a support layer hardly soluble or insoluble in water comprising **ethyl cellulose and hydroxylpropyl cellulose**, as recited in amended claim 1. Kim et al. merely disclose a usual backing layer. Specifically, this reference teaches an impenetrable base, such as a plastic sheet like polyethylene, nylon, a nonwoven fabric, etc. (see page 15, line 30 - page 16, line 10).

Moreover, the invention of Kim et al. relates to a transdermal drug delivery composition comprising a hydrophilic polymer base, a drug, a lipophilic permeation enhancer and a compatibilizer consisting essentially of an **acrylate polymer** which compatibilizes the lipophilic enhancer with the hydrophilic polymer base, and which renders the composition thermodynamically stable (see claim 1 of the reference).

As a problem to be solved, Kim et al. teach that "a technique of preparing **an uniform, stable,** hydrogel composition for transdermal drug delivery, which includes **both a hydrophilic component,** i.e. a hydrophilic polymer base, and **lipophilic substances,** i.e. permeation enhancers, is needed" (emphasis added) (see page 3, lines 26-29).

As a means for solving the above problem, Kim et al. describe that their invention is based on the discovery that a stable hydrogel composition can be formulated for transdermal delivery of drugs, wherein **an acrylate polymer** is used as a compatiblizer which compatibilizes the lipophilic component (i.e., the enhancer) with the hydrophilic polymer base, rendering a uniform composition that is **thermodynamically stable** (see page 8, lines 20-24).

The hydrogel composition of Kim et al. comprises, for example, the following ingredients: (1) a hydrophilic polymer base (such as PVP, PYA, maleic anhydride/vinyl ether copolymer, etc.); (2) a drug; (3) a lipophilic permeation enhancer (such as a saturated fatty acid, an unsaturated fatty acid, an ester thereof, etc.); (4) a compatibilizer consisting of an acrylate polymer (such as acrylic acid polymer, methacrylic acid polymer, alkyl acrylate polymer, alkyl methacrylate polymer, copolymer thereof, etc.); and (5) water as a solvent (see page 8, last line - page 9, line 10).

As mentioned above, and as described in Kim et al., the hydrogel composition contains a hydrophilic compound, a lipophilic compound **and** a compatibilizer selected from **an acrylate polymer** in order to compatibilize both compounds as essential ingredients, as well as an active drug.

On the other hand, the drug layer of the present invention contains methyl vinyl ether-maleic anhydride copolymer as an adhesive agent, and HPC, HPMC or HEC as a thickener. A compatibilizer, such as **an acrylate polymer,** is not contained therein (claim 6), and does not need to be contained therein.

According to Kim et al., as mentioned above, by compartibilizing both a hydrophilic substance and a lipophilic substance using an acrylate polymer, the desired effects, namely stable and uniform hydrogel, can be attained. Therefore, the transdermal drug delivery composition disclosed in the Kim et al. reference is different from the patch of claim 1.

Brantl et al.

Brantl et al. do not teach or suggest a support layer hardly soluble or insoluble in water comprising ethyl cellulose and hydroxypropyl cellulose, as recited in claim 1. The reference describes that a support layer may be provided between a reservoir layer and the backing layer (see column 4, lines 13-17). However, the support layer consists of a laminate of a thin aluminum foil and a polyethylene film. Thus, the support layer is different from that of the present invention. Accordingly, Brantl et al. do not cure the deficiencies of Kim et al.

McQuinn

McQuinn also does not disclose a support layer hardly soluble or insoluble in water comprising ethyl cellulose and hydroxypropyl cellulose. Moreover, this reference relates to a method of measuring the blood level of a drug in a mammal by adhering a device, such as a patch being free of a drug to a mucosal surface of the mammal. Therefore, the reference is not analogous to the present invention. In addition, McQuinn does not teach or suggest the backing layer of claim 1.

Conclusion Regarding Claims 1, 4 and 6

In view of the foregoing, the patch of claim 1 would not have been rendered obvious by the Kim et al., Brandtl et al. and McQuinn references. Claims 4 and 6 depend from claim 1, and thus also would not have been rendered obvious by the references. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

Claims 2, 3 and 5

The Examiner also rejects claim 2 under 35 U.S.C. § 103(a) as being unpatentable over Kim et al. in view of Brantl et al., and further in view of McQuinn, and further in view of Yamaguchi et al. (U.S. 5,820,877); rejects claim 3 under 35 U.S.C. § 103(a) as being unpatentable over Kim et al. in view of Brantl et al., and further in view of McQuinn, and further in view of Miller, II et al. (U.S. 2004/0086551); and rejects claim 5 under 35 U.S.C. § 103(a) as being unpatentable over Kim et al. in view of Brantl et al., and further in view of McQuinn, and further in view of Yamaguchi et al., and further in view of Miller, II et al. Applicants respectfully traverse the rejections.

The arguments above with respect to Kim et al., Brantl et al. and McQuinn are equally applicable to these rejections. Yamaguchi et al. and Miller, II et al. do not cure the deficiencies identified above. Therefore, claim 1 would not have been obvious over the applied references. Claims 2, 3 and 5 depend directly or indirectly from claim 1, and thus also would not have been obvious over the references. Accordingly, reconsideration and withdrawal of the rejections are respectfully requested.

III. Conclusion

Therefore, in view of the foregoing amendments and remarks, it is submitted that each of the grounds of rejection set forth by the Examiner has been overcome, and that the application is in condition for allowance. Such allowance is solicited.

Respectfully submitted,

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